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EXTENDED REPORT

Weight loss for overweight and obese individuals with gout: a systematic review of longitudinal studies

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ABSTRACT

Objectives Weight loss is commonly recommended for gout, but the magnitude of the effect has not been evaluated in a systematic review. The aim of this systematic review was to determine benefits and harms associated with weight loss in overweight and obese patients with gout.

Methods We searched six databases for longitudinal studies, reporting the effect of weight loss in overweight/obese gout patients. Risk of bias was assessed using the tool Risk of Bias in Non-Randomised Studies of Interventions. The quality of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation.

Results From 3991 potentially eligible studies, 10 were included (including one randomised trial). Interventions included diet with/without physical activity, bariatric surgery, diuretics, metformin or no intervention. Mean weight losses ranged from 3 kg to 34 kg. Clinical heterogeneity in study characteristics precluded meta-analysis. The effect on serum uric acid (sUA) ranged from -168 to 30 µmol/L, and 0%–60% patients achieving sUA target (<360 µmol/L). Six out of eight studies (75%) showed beneficial effects on gout attacks. Two studies indicated dose–response relationship for sUA, achieving sUA target and gout attacks. At short term, temporary increased sUA and gout attacks tended to occur after bariatric surgery.

Conclusions The available evidence is in favour of weight loss for overweight/obese gout patients, with low, moderate and low quality of evidence for effects on sUA, achieving sUA target and gout attacks, respectively. At short term, unfavourable effects may occur. Since the current evidence consists of a few studies (mostly observational) of low methodological quality, there is an urgent need to initiate rigorous prospective studies (preferably randomised controlled trials).

Systematic review registration PROSPERO, CRD42016037937.

INTRODUCTION

Gout is a common form of inflammatory arthritis,^{1 2} with an age-standardised global prevalence of 0.08% and is higher in developed countries.³ Gout is a crystal-deposition disease resulting from chronic elevation of serum uric acid (sUA) above the saturation point for monosodium urate (MSU).^{4–7} Initial presentation is severely painful episodes of peripheral joint synovitis (acute ‘attacks’), but joint damage

and subcutaneous tophus deposition may develop.⁸ The general management principle is to reduce sUA levels, allowing MSU crystals to dissolve, leading to the elimination of acute attacks, disappearance of tophi and possibly cure of the disease.^{9–11}

Body mass index (BMI) is strongly positively correlated to sUA levels,^{12 13} and weight loss is a commonly recommended treatment for gout.^{14–23} Furthermore, weight loss from bariatric surgery is associated with reduced incidence of hyperuricaemia and gout.²⁴ The mechanism by which weight loss can lower sUA levels is poorly understood. Some suggest that improved insulin resistance results in less insulin-enhanced reabsorption of organic anions such as urate,² and a study demonstrated decreased sUA in overweight patients receiving either weight loss from low-energy diet or an insulin-sensitising agent.²⁵ However, a study of severe obese patients receiving bariatric surgery found no association between reduced sUA levels and improved insulin resistance,²⁶ making a relationship questionable.

Guidelines recommending weight loss for gout patients^{14–23} are based on evidence from only few clinical studies,^{27 28} one population-based study²⁹ and indirect evidence from studies on non-gout subjects. The evidence for effectiveness in clinical studies has to our knowledge not previously been evaluated in a systematic review. Therefore, the primary objective of this systematic review was to determine the benefits and harms associated with weight loss in overweight and obese individuals with gout. Furthermore, we had an explicit focus on the weight loss intervention (including magnitude and intensity) to see whether a dose–response relationship exists at the study (ie, group) level.

METHODS

Protocol

A protocol adhering to the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols 2015 statement³⁰ was registered online (PROSPERO: CRD42016037937) and published on www.parkerinst.dk.

Search strategy

We searched four bibliographic databases on 26 April 2016; MEDLINE via Ovid from 1946, EMBASE via Ovid from 1974, Web of Science via Web of Knowledge from 1900, Cochrane Central



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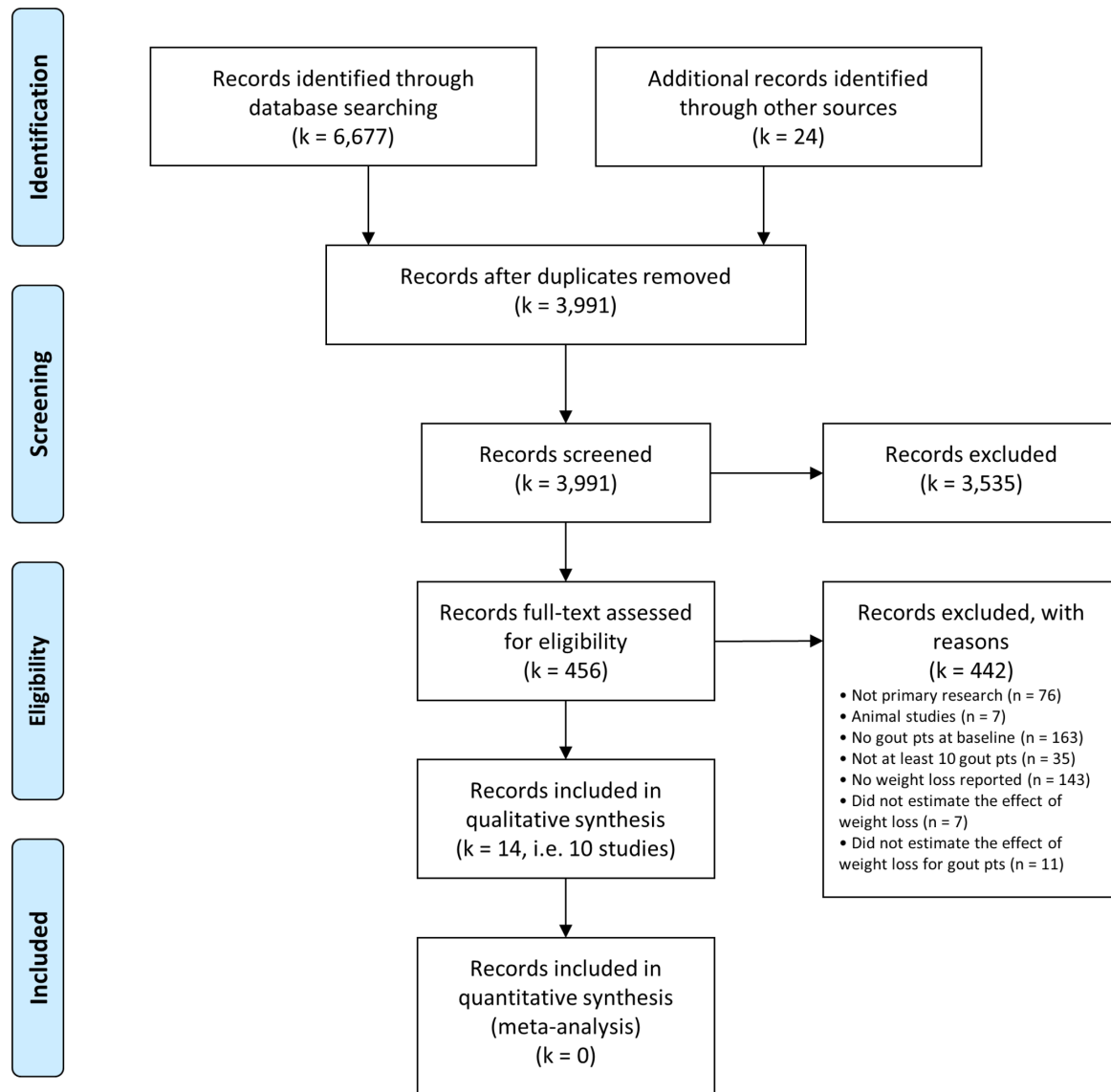


Figure 1 PRISMA flow diagram. Modified from Moher *et al.*⁷⁵ pts, patients.

Register of Controlled Trials (CENTRAL, The Cochrane Library), as well as ClinicalTrials.gov and WHO International Clinical Trial Registry Platform portal (search strategy presented: online supplementary text S1). We screened reference lists of relevant articles, as well as the American College of Rheumatology (ACR) and European League Against Rheumatism conference abstracts from 2014 and 2015, the ACR conference abstracts from 2016 and content experts were asked if they were aware of any other relevant studies.

Study selection

Anticipating only few randomised controlled trials (RCTs), we also included longitudinal observational studies (non-randomised studies) that quantitatively estimated the effect following weight loss. Studies needed to include ≥ 10 adult and overweight/obese patients (author described or BMI ≥ 25 kg/m²³¹) with diagnosed gout (author described or meeting the 1977 ACR criteria for gout³²). Eligible interventions included those where a weight reduction was reported explicitly, whether intentional or unintentional. The weight reduction was required to be the only difference in terms of intervention from the defined control group. Two reviewers (SMN supported by EMB) assessed the

records. Disagreements were resolved by consensus or by discussion with a third reviewer (RC).

Data extraction and management

Two reviewers (SMN supported by RC) extracted the data. Prespecified outcomes included essential outcome domains for chronic gout^{33 34}: (1) joint pain; (2) tophus/tophi; (3) physical function; (4) health-related quality of life (HRQoL); (5) sUA change; (6) Achieving sUA target (ie, sUA reduction to <360 μ mol/L (6 mg/dL)); (7) serious adverse events (SAEs, defined as adverse events that are fatal, life-threatening or require hospitalisation); (8) withdrawals due to adverse events (WDdtAEs); (9) patient global assessment; (10) body weight change; and (11) gout attacks (any measure).

Assessment of risk of bias in included studies (internal validity)

Two reviewers (SMN supported by RC) assessed risk of bias using the tool Risk of Bias In Non-Randomised Studies of Interventions^{35 36} for evaluation of the risk of bias in non-randomised studies comparing health effects of two or more interventions.

Table 1 Characteristics of the included studies

| Author, year, (multiple publication) | Study characteristics | | Characteristics of gout pts | | | | | | |
|--|---|--|-----------------------------|----------------|-----------------------------|--------------------------|--------------------------|--------------------------------------|--------------------------|
| | Study population | Intervention | No. of pts | Females, n pts | Age, years | BMI, kg/m ² | Disease duration, years | Urate-lowering medication use, n pts | Presence of tophi, n pts |
| Nguyen <i>et al.</i> 2016 ⁴⁴ (Sherwin <i>et al</i> 1981 ⁴⁷) | Men with a high cardiovascular risk profile and no gout at baseline of the MRFFIT* study (n=11 896). 408 developed gout during the 7-year follow-up period. | This substudy of MRFFIT uses a subpopulation, stratifying the risk of recurrent gout attacks for the BMI change in gout pts. | 408† | 0 (0) | NA | NA | NA | NA | NA |
| Dalbeth <i>et al.</i> 2014 ²⁷ (Dalbeth, <i>et al</i> 2013 ⁴⁶) | Pts with T2D and BMI ≥35 kg/m ² who met presurgery weight loss requirements during part 1 (72 included, 60 completed). Included gout pts. | (Part 1) Presurgery weight loss (dietetic advice, set goals to establish a regular exercise programme and lose 5–10 kg, in addition to Optifast VLCD programme 4 weeks prior to surgery). (Part 2) Bariatric surgery (laparoscopic sleeve gastrectomy) | 12 | 5 (42) | 49 (8) | 48.5 (5.4) | 6.4 (7) | 9 (75) | NA |
| Romero-Talamás <i>et al.</i> 2014 ⁴⁶ | Gout pts with obesity (n=155). | I: Bariatric surgery (Roux-en-Y gastric bypass, gastrectomy, or adjustable gastric banding) C: Non-bariatric surgery (laparoscopic cholecystectomy, open cholecystectomy, cholecystectomy with another contaminant procedure or laparoscopic Heller myotomy). | 99 | 75 (75) | 52.1 (10.3) | 49.5 (11.9) | NA | 53 (56) | NA |
| Zeng <i>et al.</i> 2012 ⁴⁹ (In Chinese, RCT) | Overweight men with gout, not using urate-lowering medication or having tophi (67 randomised, 61 completed the study). | I: High protein C: Low purine | 30 31 | 0 (0) 0 (0) | 61.5 (14.5) 61.3 (11.2) | 27.0 (1.3) 27.2 (1.6) | NA NA | 0 (0) 0 (0) | 0 (0) 0 (0) |
| Perez-Ruiz <i>et al.</i> 2011 ⁴⁵ (unpublished data) | Gout pts with 5 years of compliance to urate-lowering therapy, and no tophi or resolution of all tophi prior to withdrawing urate-lowering therapy (n=211). | Withdrawal of urate-lowering therapy, stratified according to weight loss: lost >5% weight Withdrawal of urate-lowering therapy, stratified according to weight loss: no weight loss | 25‡ 167‡ | 1 (4) 7 (4) | NA NA | NA NA | 7.4 (6.4) 7.2 (6.4) | 25 (100) 167 (100) | 0 (0) 0 (0) |
| Zhu <i>et al.</i> 2010 ⁴⁰ (Sherwin, <i>et al</i> 1981 ⁴⁷) | Men with a high cardiovascular risk profile and sufficient data from the MRFFIT* study (n=12 379). Included gout pts. | This substudy of MRFFIT uses a subpopulation, stratifying the changes in sUA for baseline BMI, weight change and other variables. | NA† | 0 (0) | NA (All: 46 (range, 35–57)) | NA | NA | NA | NA |
| Baskova <i>et al.</i> 2009 ⁴⁰ (In Russian) | Gout pts (30 included, 23 completed). | Metformin (1500mg/day) | 23 | 2 (7) | 51 (range, 43–54) | 32.6 (5.2) | 6 (range, 4–11) | 0 (0) | 8 (27) |
| Friedman <i>et al.</i> 2008 ⁴³ | Pts received gastric bypass and experiencing postoperative gout attacks. | Bariatric surgery (gastric bypass and preoperative preparation, that is, clear liquid diet with protein supplementation 4–7 days and mechanical bowel preparation 2 days). | 21 | 6 (29) | 52 (range, 32–73) | 49.6 (range, 36.1–63) | NA | NA | NA |
| Dessein <i>et al.</i> 2000 ²⁸ (Terkeftaub, <i>et al.</i> 2001 ⁴⁸) | Gout pts, without tophi (n=13). | Diet recommendations (calorie restriction with specified macronutrient proportions, replacing refined carbohydrates with complex ones and replacing saturated fats with monosaturated and polyunsaturated ones). | 13 | 0 (0) | 50§ (5.6; range, 38–62) | 30.5§¶ (8.1) | 7§ (10.2; range, 0.5–38) | 0 (0) | 0 (0) |
| Brandstetter <i>et al.</i> 1986 ⁴¹ (In German) | Gout pts with hypertension (n=22) | I: Allopurinol, diet (low purine) and celiprolol (betablocker) and chlorthalidone (diuretic). C: Allopurinol, diet (low purine) and celiprolol . | 11+11 (both groups) | 7 (32) | 52§ (range, 28–68) | 26.0** | NA | NA | NA |

The results are reported as mean (SD) or number (%), unless otherwise indicated.

*The original study (MRFFIT)³⁹ randomised pts (n=12 866) to intervention (smoking cessation, weight reduction by caloric intake reduction and increased physical activity, nutritional counselling and antihypertensive treatment) or control.

†May include gout pts that were not overweight at baseline.

‡Due to loss of data in the study, the number of pts in the groups were 25 and 167 at baseline, and 29 and 163 at latest follow-up.

§Median.

¶One had normal BMI.

**No BMI were reported, so BMI were calculated from data on height (median, 179 (range, 162–199)), and weight (median, 83.2 (range, 58–105)).

Allopurinol, diet (low purine) and celiprolol.

BMI, body mass index; C, control treatment; I, intervention; MRFFIT, The Multiple Risk Factor Intervention Trial; NA, no data available; pts, patients; RCT, randomised controlled trial; sUA, serum uric acid; T2D, type 2 diabetes.

Post hoc, we decided to also use this tool for assessing studies with only one study group, by assuming that a virtual control group not receiving any intervention and experiencing no effect on any outcome was available, and for assessing RCTs, making comparisons possible. We resolved disagreements by discussion.

Important confounders of interest and cointerventions possibly affecting the effect of weight loss were not specified at protocol stage but prior to the risk of bias assessment (online supplementary text S2).

Reporting bias in individual studies was further investigated by comparing the constructed outcome reporting matrix,³⁷ with the protocols (if available).

Statistical analyses and evidence synthesis

None of our planned meta-analyses were conducted due to indisputable clinical heterogeneity in study characteristics (PICOTs). Instead it was decided post hoc that data for each study would be presented for all time points in a summary of findings table and the latest time point as changes from baseline would be summarised for each study in a summary of findings and GRADE evidence profile table. Based on the tables, we qualitatively considered the impact of follow-up time, that is, short-term (<3 months), medium (3–12 months) and long-term (>12 months), acute versus chronic gout, presence versus absence of concurrent urate-lowering medication use, presence versus absence of tophi, the dose–response phenomena of weight loss in magnitude and intensity (ie, magnitude over time) and the impact of bias. A graph showing the relationship between weight loss and sUA was constructed post hoc.

Dealing with missing data

Where data were missing or incomplete, we searched for information from the study authors and from additional records for the study. No imputations were carried out for patients lost at follow-up. Missing body weights were estimated from BMI, assuming a height of 1.70 m. Missing SDs were calculated from other statistics such as standard errors, or estimated from other studies investigating gout patients; for sUA, we used a SD for change from baseline of 137 $\mu\text{mol/L}$.

Assessing the quality of the evidence

We assessed the quality of the evidence with the GRADE approach,³⁸ starting at low quality of evidence, since the evidence was primarily based on observational studies and subsequently down-rated or up-rated the evidence.

RESULTS

Study selection

We identified 3991 records after removal of duplicates, forwarding 456 for full-text assessments after screening (figure 1). After excluding 442 records (see online supplementary text S3), we identified 14 records describing 10 studies for inclusion in the systematic review.^{27–29 39–49}

During the study selection and data extraction, authors of 18 studies^{27–29 40 43–46 49–58} were contacted; three responded^{27 44 45} and provided additional information, including unpublished data for Perez-Ruiz *et al.*⁴⁵

Study characteristics

The studies were comprised of one RCT⁴⁹ and nine non-randomised studies (table 1). Gout patients were a subgroup in three of the studies,^{27 29 44} of which one study initially only included non-gout patients but did a subanalysis on recurrent gout attacks

for those who developed gout during follow-up.⁴⁴ The studies included between 12 and 408 gout patients, including 0%–75% females. The average age and BMI ranged from 49 to 63.3 years, and 26.0 to 49.6 kg/m^2 , respectively. Case definitions of gout included the use of the 1977 ACR criteria in one study,⁴² diagnosis confirmed by detecting crystals in three studies,^{28 40 45} asking ‘Have you been told by your physician that you have gout?’ in two studies,^{29 44} medical history and documentation of previous gout attacks in one study,⁴³ documented episode(s) or evidence of medication use in one study,⁴⁶ or not specified in two studies^{41 49} (online supplementary table S1). Comorbidities selected in the studies, besides overweight, included type 2 diabetes,²⁷ hypertension⁴¹ and a high cardiovascular risk profile.^{29 44}

Interventions included intentional weight loss from dietary changes with or without increased physical activity,^{27 28} bariatric surgery^{27 43 46} and unintentional weight loss from high protein diet,⁴⁹ diuretics⁴¹ and metformin.⁴⁰ Three studies^{29 44 45} stratified according to weight or BMI reduction, using no reduction as control. Four studies had no control group.^{27 28 40 43} Follow-up ranged from 4 weeks to 7 years, and a mean weight loss of 3–34 kg at latest follow-up was reported.

Effect of weight loss

No data were available for joint pain, HRQoL or patient global assessment (outcome matrix: online supplementary table S2). One study⁴⁵ provided data on tophi, reporting none for both groups at baseline and follow-up, and one study²⁷ provided data on physical function measured by Short Form-36 physical functioning domain, reporting diminished function with the values 43.3 (SD 21.8), 24.6 (SD 28.2), 10.8 (SD 12.8) at baseline, 6 months and 1.5 years, respectively. One study⁴⁰ reported four WDdtAEs from metformin, and one study²⁷ did not report any SAEs in gout patients. On sUA, achieving sUA target and gout attacks, eight, five, and eight studies provided data, respectively (table 2).

The effect on mean sUA ranged from $-168 \mu\text{mol/L}$ to 30 $\mu\text{mol/L}$ (-2.8 mg/dL to 0.5 mg/dL) at latest follow-up (table 3). Studies with the largest (and fastest) weight loss showed in general the largest decrease (figure 2).^{27 28 46} Furthermore, a dose–response relationship was shown by Zhu *et al.*²⁹ with a weight loss of $\geq 10 \text{ kg}$ being associated with a change in sUA of $-37 \mu\text{mol/L}$. It should be noted that non-gout and non-overweight patients were included in their analysis as well. At short term, Dalbeth *et al* (part 2)²⁷ reported an immediate postoperative mean sUA of 510 (SD 130) $\mu\text{mol/L}$, that is, an increase of 70 $\mu\text{mol/L}$ from bariatric surgery, and at latest follow-up, sUA had dropped to 330 (SD 90) $\mu\text{mol/L}$. In that period, three out of seven patients terminated urate-lowering medication, that is, the decrease may truly be larger. Three studies showed no effect on sUA; Perez-Ruiz *et al.*⁴⁵ and Dalbeth *et al* (part 1),²⁷ both with a concurrent decrease in urate-lowering medication, and Brandstetter *et al.*,⁴¹ where the weight loss may partly be due to diuretics and hence truly lower. Barskova *et al.*⁴⁰ showed a decrease in sUA from a weight loss of only 3 kg. However, the use of metformin can have affected the results.

The proportion achieving sUA target ($<360 \mu\text{mol/L}$) ranged from 0% to 60% reduction in patients with raised sUA. Furthermore, a dose–response relationship was shown by Zhu *et al.*²⁹ with approximately three times higher odds of achieving sUA target with loss of $\geq 10 \text{ kg}$ body weight during 7 years compared with not losing weight. It should be noted that non-overweight gout patients were included in their analysis as well. The 0% and

Table 2 Study findings

| Author, year, (multiple publication) | Group: time point | Body weight, kg | Body weight change from baseline, kg | sUA, $\mu\text{mol/L}$ | Achieving sUA target*, n pts | Gout attacks |
|---|-------------------------------------|---------------------------|--------------------------------------|--|--------------------------------------|--|
| Nguyen et al, 2016 ⁴⁴ (Sherwin et al 1981 ⁴⁵) | <-5% BMI: 12 months | NA | NA | NA | NA | Recurrent, OR 0.61 (0.32 to 1.16) [†] |
| | -3.6 to -5% BMI: 12 months | NA | NA | NA | NA | Recurrent, OR 0.94 (0.43 to 2.06) [†] |
| | No change: 12 months | NA | NA | NA | NA | Recurrent, OR 1.00 (reference) [†] |
| | +3.6 to +5% BMI: 12 months | NA | NA | NA | NA | Recurrent, OR 1.43 (0.75 to 2.72) [†] |
| | >+5% BMI: 12 months | NA | NA | NA | NA | Recurrent, OR 1.60 (0.89 to 2.89) [†] |
| Dalbeth et al, 2014 ²⁷ (Dalbeth et al 2013 ⁴²) | Baseline (part 1) | 139.8 (23.8) | - | 410 (70) | 2 (17) | 2 (17) pts had ≥ 1 in 3 months |
| | 6 months (part 1/2) | 134.3 (24.3) | -5.5 (5.2) | 440 (90) | 2 (17) | 0 (0) pts had ≥ 1 in 6 months |
| | 6 months, 2 weeks (part 2) | NA | NA | 510 (130) | NA | NA |
| | 1.5 years (part 2) | 100.3 (16.3) | -34 (11.0) | 330 (90) | 8 (67) | 3 (25) pts had ≥ 1 in follow-up |
| | I: Baseline | 143# | - | 546 (120) | NA | 20 (24) pts had ≥ 1 in 12 months |
| Romero-Talamás et al, 2014 ⁴⁶ | I: 1 month | 132# | -11# | NA | NA | NA (18) pts had ≥ 1 in 1 month |
| | I: 13 months | 101# | -31# | 336 (150) | NA | NA (8) pts had ≥ 1 in 12 months |
| | C: Baseline | 106# | - | 462 (120) | NA | 10 (18) pts had ≥ 1 in 12 months |
| | C: 1 month | 105# | -1# | NA | NA | NA (2) pts had ≥ 1 in 1 month |
| | C: 13 months | 104# | -2# | 420 (96) | NA | NA (11) pts had ≥ 1 in 12 months |
| | I: Baseline | 74.5 (3.50) | - | 486 (41) | NA | All (100) had ≥ 1 in 6 months; 33 episodes |
| | I: 6 months | 65.8 (4.44) | -8.7 | 420 (37) | NA | 17 episodes; 48% fewer gout attacks |
| Zeng et al, 2012 ⁴⁹ (In Chinese) | C: Baseline | 72.7 (3.26) | - | 486 (41) | NA | All (100) had ≥ 1 in 6 months; 36 episodes |
| | C: 6 months | 69.3 (7.78) | -3.4 | 467 (42) | NA | 28 episodes; 22% fewer gout attacks |
| | Lost weight: baseline | 81.0 (11.0) | - | 263 (59) | 23 (92) | 0 (0) pts with gout attacks at withdrawal |
| | Lost weight: mean 34 (26) months | 77.8 (11.0) | -3.2 (5.6) | 298 (59) | 27 (93) | 5 (17) pts with gout attacks during follow-up |
| | No weight loss: baseline | 81.9 (8.6) | - | 491 (95) | 150 (90) | 0 (0) pts with gout attacks at withdrawal |
| Perez-Ruiz et al, 2011 ⁴⁵ (unpublished data) | No weight loss: mean 32 (28) months | 84.3 (9.9) | 2.4 (4.3) | 509 (90) | 146 (90) | 80 (49) pts with gout attacks during follow-up |
| | ≤ -10 kg: 7 years | NA | (range, ≤ -10) | Change, -37 (-40 to -35) ^{††} | OR 3.19 (1.99 to 5.09) ^{**} | NA |
| | -5 to -9.9 kg: 7 years | NA | (range, -9.9 to -5) | Change, -19 (-20 to -17) ^{††} | OR 2.33 (1.75 to 3.11) ^{**} | NA |
| | -1 to -4.9 kg: 7 years | NA | (range, -4.9 to -1) | Change, -7 (-9 to -6) ^{††} | OR 1.53 (1.24 to 1.89) ^{**} | NA |
| | No change: 7 years | NA | (range, -0.9 to 0.9) | Change, 0 (reference) ^{††} | OR 1.0 (reference) ^{**} | NA |
| Zhu et al, 2013 ²⁹ (Sherwin et al 1981 ⁴⁵) | +1 to +4.9 kg: 7 years | NA | (range, 1 to 4.9) | Change, 5 (4 to 7) ^{††} | OR 1.01 (0.80 to 1.27) ^{**} | NA |
| | +5 to +9.9 kg: 7 years | NA | (range, 5 to 9.9) | Change, 17 (16 to 19) ^{††} | OR 0.65 (0.45 to 0.95) ^{**} | NA |
| | $\geq +10$ kg: 7 years | NA | (range, ≥ 10) | Change, 26 (23 to 29) ^{††} | OR 0.58 (0.31 to 1.08) ^{**} | NA |
| | Baseline | 94# | - | 570 (110) | 0 (0) | 3 ^{††} (range, 1 to 6) pr. patient in 12 months |
| | 6 months | 91# | -3# | 435 (91) | NA | NA |
| Barskova et al, 2009 ⁴⁰ (In Russian) | 12 months | 91# | -3# | 443 (107) | 11 (48) | 1 ^{††} (range, 0-2) pr. patient in 12 months |
| | Baseline | 143# | - | NA | NA | NA |
| | 6 months | NA | NA | NA | NA | 7 (33%) pts had an attack during 6 months |
| Friedman et al, 2008 ⁴³ | Baseline | 91.1 ^{††} (23.5) | - | 570 ^{††} (100) | 1 (8) ^{††¶} | 2.1 ^{††} (SD, 0.8) pr. month (in 4 months) |
| | 6 months | 83.4 ^{††} (22.0) | -7.7 ^{††} (range: 0 to -21) | 470 ^{††} (90) | 7 (54) ^{††¶} | 0.6 ^{††} (SD, 0.7) pr. month |
| | 16 weeks | | | | | |

Continued

Table 2 Continued

| Author, year, (multiple publication) | Group: time point | Body weight, kg | Body weight change from baseline, kg | sUA, $\mu\text{mol/L}$ | Achieving sUA target*, n pts | Gout attacks |
|--|-------------------|-----------------|--------------------------------------|------------------------|------------------------------|--------------|
| Brandtetter <i>et al</i> , 1986 ⁴¹ (In German) | I: Baseline | 89.9 (10.9) | – | 316 (46) | NA | NA |
| | I: 4 weeks | 89.1 (10.6) | –0.8 | 368 (55) | NA | NA |
| | I: 3 months | 87.3 (9.6) | –2.6 | 364 (29) | NA | NA |
| | I: 6 months | 84.2 (8.4) | –5.7 | 320 (61) | NA | NA |
| | C: Baseline | 77.0 (14.0) | – | 297 (54) | NA | NA |
| | C: 4 weeks | 77.0 (13.8) | 0 | 304 (98) | NA | NA |

The results are reported as means (SD) or number (%), unless otherwise indicated.

*Achieving sUA target, that is, sUA <360 $\mu\text{mol/L}$ (6 mg/dL).

†Multivariable OR of recurrent gout attacks according to BMI change. Based on a conditional logistic regression adjusted for BMI, age, education, alcohol and coffee intake, presence of hypertension and diuretic use measured during the 12 months before the incident gout attack. It should be noted that non-overweight gout patients were included as well in the analysis.

‡Estimated from the BMI assuming a height of 1.70 m.

§Due to loss of data, the number of patients in the groups were 25 and 167 at baseline, and 29 and 163 at last follow-up.

¶Note that Dessein *et al* uses a cut-off of ≤ 510 $\mu\text{mol/L}$.

**Multivariable OR of achieving sUA target of ≤ 360 $\mu\text{mol/L}$ according to the weight loss. Based on a conditional logistic regression adjusted for time-varying covariates, that is, age, congestive heart failure, hypertension, diuretic use, serum creatinine level, alcohol intake and dietary variables (intake of fructose, caffeine, total protein, polyunsaturated fat, monounsaturated fat, saturated fat and fibre). Reported with corresponding 95% CIs. It should be noted that non-overweight gout patients were included as well in their analysis.

††Median.

‡‡Based on linear mixed model adjusted for baseline covariates (race, education level and weight categories), and time-varying covariates, that is, age, congestive heart failure, hypertension, diuretic use, serum creatinine level, alcohol intake and dietary variables (intake of fructose, caffeine, total protein, polyunsaturated fat, monounsaturated fat, saturated fat and fibre). Reported with corresponding 95% CIs. It should be noted that non-overweight and non-gout patients were included as well in their analysis.

AEs, adverse events; BMI, body mass index; I, intervention group; C, control group; n, number; pts, patients; sUA, serum uric acid.

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Table 3 Summary of findings and GRADE evidence profile

| Quality assessment | | | | | | | | | | Effect | | Quality | | | |
|--|-------------------|---------------|--------------|-------------|----------------------------|-----------------|--------------------|-------------------------|--|--|-------------------------|---|---|----------|--------------|
| Studies with data | Study limitations | Inconsistency | Indirectness | Imprecision | Publication bias | | Other | Study | No. of patients | | Weight loss information | | Effect | | GRADE rating |
| | | | | | Weight loss/No weight loss | Weight loss, kg | | | Weight loss pr. month (% of body weight) | Weight loss pr. month (% of body weight) | Overall conclusion | | | | |
| Serum uric acid (µmol/L) | | | | | | | | | | | | | | | |
| 7 | Serious (−1) | Not serious | Not serious | Not serious | Not serious | | Dose response (+1) | Nguyen Dalbeth (part 1) | NA/NA | – | – | NA | Weight loss results in a decrease of sUA after medium/long follow-up. | Low | ⊕○○○ |
| | | | | | | | | Dalbeth (part 2) | 12/0 | 5.5 kg (3.9) | 0.9 kg (0.7) | 30* (−48 to 108) | | | |
| | | | | | | | | Romero-Talamás | 99/56 | 34 kg (24.3) | 2.8 kg (2.0) | −110* (−188 to −32) | | | |
| | | | | | | | | Zeng | 30‡/31 | 29 kg† (23) | 2.4 kg (1.8) | −168 (−213 to −123) | | | |
| | | | | | | | | Perez-Ruiz | 25§/167§ | 3.6 kg (4.8) | 0.6 kg (0.8) | −47 (−66 to −27) | | | |
| | | | | | | | | Zhu | NA/NA | 5.6 kg (6.9) | 0.2 kg (0.2) | 17 (−40 to 73) | | | |
| | | | | | | | | | | – | – | Dose–response relationship between weight change and sUA change¶ | | | |
| | | | | | | | | Barskova | 23‡/0 | 3 kg† (3.2) | 0.3 kg (0.3) | −127* (−183 to −71) | | | |
| | | | | | | | | Friedman | 21/0 | NA | NA | NA | | | |
| | | | | | | | | Dessein | 13/0 | 7.7 kg** (8.4) | 2.1 kg (2.3) | −100*†† (−174 to −26) | | | |
| | | | | | | | | Brandstetter | 11‡/11 | 5.7 kg (6.9) | 1.0 kg (1.1) | −2 (−116 to 113) | | | |
| Achieving serum uric acid target that is, sUA<360 µmol/L | | | | | | | | | | | | | | | |
| 4 | Serious (−1) | Not serious | Not serious | Not serious | Not serious | | Large effect (+1) | Nguyen Dalbeth (part 1) | NA/NA | – | – | NA | Weight loss results in a higher chance of achieving sUA target after medium/long follow-up. | Moderate | ⊕⊕○ |
| | | | | | | | Dose response (+1) | Dalbeth (part 2) | 12/0 | 5.5 kg (3.9) | 0.9 kg (0.7) | 0% (0/10) reduction in pts with raised sUA* | | | |
| | | | | | | | | | 12/0 | 34 kg (24.3) | 2.8 kg (2.0) | 60% (6/10) reduction in pts with raised sUA* | | | |
| | | | | | | | | Romero-Talamás | 99/56 | 29 kg† (23) | 2.4 kg (1.8) | NA | | | |
| | | | | | | | | Zeng | 30‡/31 | 3.6 kg (4.8) | 0.6 kg (0.8) | NA | | | |
| | | | | | | | | Perez-Ruiz | 25§/167§ | 5.6 kg (6.9) | 0.2 kg (0.2) | 1% reduction in pts with raised sUA | | | |
| | | | | | | | | Zhu | NA/NA | – | – | Dose–response relationship between weight change achieving serum uric acid target** | | | |
| | | | | | | | | Barskova | 23‡/0 | 3 kg† (3.2) | 0.3 kg (0.3) | 48% (11/23) reduction in pts with raised sUA* | | | |
| | | | | | | | | Friedman | 21/0 | NA | NA | NA | | | |
| | | | | | | | | Dessein | 13/0 | 7.7 kg** (8.4) | 2.1 kg (2.3) | 50% (6/12) reduction in pts with raised sUA*‡‡ | | | |
| | | | | | | | | Brandstetter | 11‡/11 | 5.7 kg (6.9) | 1.0 kg (1.1) | NA | | | |

Table 3 Continued

| Table 3 Continued | | | | | | | | | | | | | | | |
|--------------------|--------------|-------------------|---------------|--------------|-------------|--------------------|-----------------|------------------|----------------------------|------------------------------------|--|---|--|--|--------------|
| Quality assessment | | | | | | | No. of patients | | | Weight loss information | | Effect | | Quality | |
| Studies with data | | Study limitations | Inconsistency | Indirectness | Imprecision | Publication bias | Other | Study | Weight loss/No weight loss | Weight loss, kg (% of body weight) | Weight loss pr. month (% of body weight) | Effect on outcome | | Overall conclusion | GRADE rating |
| Gout attacks | | | | | | | | | | | | | | | |
| 8 | Serious (−1) | Not serious | Not serious | Not serious | Not serious | Dose response (+1) | | Nguyen | NA/NA | – | – | Dose–response relationship between BMI change and recurrent gout attacks** | | Weight loss results in fewer gout attacks after medium/long follow-up. | Low ⊕○○ |
| | | | | | | | | Dalbeth (part 1) | 12/0 | 5.5 kg (3.9) | 0.9 kg (0.7) | 0 pts had ≥1 attack 6 months (At baseline two pts had ≥1 attack in 3 months)* | | | |
| | | | | | | | | Dalbeth (part 2) | 12/0 | 34 kg (24.3) | 2.8 kg (2.0) | Three pts had ≥1 attack in 12 months (At baseline for part 2, 0 pts had ≥1 attack in 6 months)* | | | |
| | | | | | | | | Romero-Talamás | 99/56 | 29 kg† (23) | 2.4 kg (1.8) | RR of 0.72 for ≥1 attack at follow-up | | | |
| | | | | | | | | Zeng | 304/31 | 3.6 kg (4.8) | 0.6 kg (0.8) | 39% fewer attacks at follow-up | | | |
| | | | | | | | | Perez-Ruiz | 255/167§ | 5.6 kg (6.9) | 0.2 kg (0.2) | RR of 0.35 for ≥1 attack at follow-up | | | |
| | | | | | | | | Zhu | NA/NA | – | – | NA | | | |
| | | | | | | | | Barskova | 234/0 | 3 kg† (3.2) | 0.3 kg (0.3) | 33% fewer attacks*†† | | | |
| | | | | | | | | Friedman | 21/0 | NA | NA | 33% (7/21) pts had attacks*§§ | | | |
| | | | | | | | | Dessein | 13/0 | 7.7 kg** (8.4) | 2.1 kg (2.3) | 71% fewer attacks*†† | | | |
| | | | | | | | | Brandstetter | 114/11 | 5.7 kg (6.9) | 1.0 kg (1.1) | NA | | | |

Modified from table made with GRADEpro (computer program on www.grade.pro.org). McMaster University, 2014. Effect on outcome was calculated as change from baseline to latest follow-up for NRS with one group, difference in changes for NRS with two groups and difference between groups at follow-up for RCTs, unless otherwise indicated. Effects on outcomes are presented as means (95% CI), numbers or RRs.

*Studies with only one group, hence the effect is not a contrast between groups.

† Weight loss estimated from BMI.

‡ On average a weight loss was seen for these pts as a group. Hence, some individuals may not have lost weight.

§ Due to loss of data in the study, the number of pts in the groups were 25 and 167 at baseline, and 29 and 163 at last follow-up, respectively. For calculation of 95% CI, a mean, that is, 26 and 165, was used.

¶ It should be noted that non-overweight and non-gout patients were included as well.

** It should be noted that non-overweight gout patients were included as well.

†† Based on medians.

‡‡ Dessein²⁹ used a cut-off of ≤510 µmol/L.

§§ For this study, no comparison (such as a comparison group or a measurement before the intervention) was provided. Hence, the number is the absolute number.

BMI, body mass index; GRADE, The Grading of Recommendations Assessment, Development and Evaluation; NRS, non-randomised study; pts, patients; RCT, randomised controlled trial; RR, risk ratio; sUA, serum uric acid.

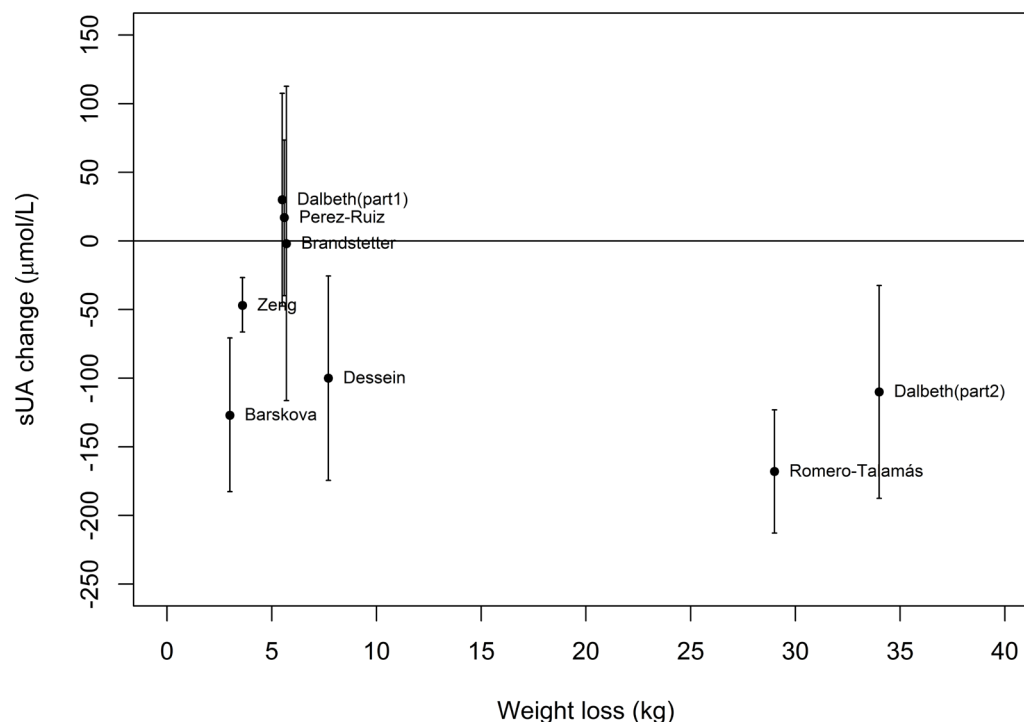


Figure 2 Relationship between weight loss and serum uric acid at latest follow-up. Estimates are shown with 95% confidence intervals. sUA, serum uric acid.

1% reduction in patients with raised sUA reported by Dalbeth *et al* (part 1)²⁷ and Perez-Ruiz *et al*,⁴⁵ respectively, are consistent with no change in sUA. Furthermore, achieving sUA target reported by Dessein *et al*²⁸ may be overestimated due to using a higher sUA cut-off of 510 μmol/L.

All studies, except two,^{27 43} with data on gout attacks, showed a beneficial effect, and Dessein *et al*²⁸ reported 71% fewer attacks. Furthermore, a dose-response relationship was shown by Nguyen *et al*.⁴⁴ It should be noted that non-overweight patients were included in their analysis as well. Dalbeth *et al* (part 2)²⁷ reported an increase from zero patients experiencing ≥1 attack during 6 months to three patients during 12 months. This is possibly due to including the immediate postoperative phase where attacks could be a consequence of the increased sUA. Likewise, Romero-Talamás *et al*⁴⁶ report a possible increase from 24% experiencing ≥1 attack during 1 year at baseline to 18% during 1 month at 1-month follow-up, and a subsequently decrease to 8% during 1 year at last follow-up.

Only one study⁴⁰ included patients with tophi at baseline, therefore the impact on tophi could not be assessed.

Risk of bias assessment

The most frequent risk of bias was 'Bias due to confounding', with four studies rated critical due to studying one group without adjustment for confounders.^{28 40 42 43} Five studies were rated serious (figure 3), and only the RCT⁴⁹ was rated low risk of bias. All studies were rated serious risk for 'Bias due to departures from intended interventions' (see possible confounders and cointerventions in online supplementary table S3). Reporting bias was suspected for two studies reporting change in BMI instead of change in weight.^{40 46} Protocols were only found for two substudies^{29 44} of one main study^{39 47} and three studies reported no published protocol.^{27 44 45}

Quality of the evidence using GRADE

For a beneficial effect of weight loss at medium-term/long-term follow-up, we evaluated the overall quality of evidence to be low for sUA, moderate for achieving sUA target and low for gout attacks.

DISCUSSION

Overall, we found low to moderate quality of evidence for beneficial effects of weight loss for overweight gout patients in terms of sUA, achieving sUA target and gout attacks. No or few data were available on our remaining prespecified outcomes. We did not find evidence for the optimal magnitude and intensity of weight loss. However, our data suggest that a weight loss of >7 kg and/or >2 kg per week from either surgery or diet results in a beneficial effect on sUA at medium-term/long-term follow-up based on three studies^{27 28 46} and that weight loss of >3.5 kg showed beneficial effects on gout attacks at medium-term/long-term follow-up based on six studies.^{27 28 40 45 46 49} However, with the present quality of evidence, further research may change these findings. WDdtAEs and SAEs were poorly reported. At short term, weight loss from bariatric surgery showed temporarily increased sUA levels and gout attacks, that is, a harmful effect, in the immediate postoperative period based on two studies.^{27 46}

It is well known that there is a higher risk of gout attacks during the first months of urate-lowering therapy, postsurgery and starvation.⁵⁹ One hypothesis is that dramatic changes in sUA, rather than absolute level, triggers gout attacks.⁶⁰ In line with this, a study⁶¹ comparing gout patients experiencing postoperative gout attacks with those who did not, find that the first group had higher presurgical sUA and a more rapid and larger decrease in sUA 3 days after surgery. Dalbeth *et al*²⁷ reported a drastic increase 2 weeks after surgery, which they suggested was due to renal dysfunction associated with major surgery, or metabolic effects from fasting or rapid weight loss (catabolic state),

| Author, year and outcome | 1. Bias due to confounding | 2. Bias in selection of participants into the study | 3. Bias in classification of interventions | 4. Bias due to departures from intended interventions | 5. Bias due to missing data | 6. Bias in measurement of outcomes | 7. Bias in selection of the reported result |
|----------------------------------|----------------------------|---|--|---|-----------------------------|------------------------------------|---|
| Nguyen, 2016* | | | | | | | |
| Gout attacks | Serious | Moderate | Moderate | Serious | Moderate | Serious | Low |
| Dalbeth, 2014* (part 1) | | | | | | | |
| Physical function, SF36 PF | Critical | Serious | Moderate | Serious | Moderate | Serious | Low† |
| sUA and achieving sUA target | Critical | Serious | Moderate | Serious | Moderate | Low | Low |
| Body weight | Critical | Critical | Moderate | Serious | Moderate | Low | Low |
| Gout attacks | Critical | Serious | Moderate | Serious | Moderate | Serious | Low |
| SAEs | Critical | Serious | Moderate | Serious | Moderate | Serious | Low |
| Dalbeth, 2014* (part 2) | | | | | | | |
| Physical function, SF36 PF | Critical | Low | Low | Serious | Moderate | Serious | Low† |
| sUA and achieving sUA target | Critical | Low | Low | Serious | Moderate | Low | Low |
| Body weight | Critical | Low | Low | Serious | Moderate | Low | Low |
| Gout attacks | Critical | Low | Low | Serious | Moderate | Serious | Low |
| Romero-Talamás, 2014 | | | | | | | |
| sUA | Serious | Low | Low | Serious | NI | Moderate | Moderate |
| Body weight (i.e. change in BMI) | Serious | Low | Low | Serious | NI | Moderate | Serious |
| Gout attacks | Serious | Low | Low | Serious | NI | Serious | Moderate |
| Zeng, 2012 | | | | | | | |
| sUA | Low | Low | Low | Serious | Moderate | Low | Moderate |
| Body weight | Low | Low | Low | Serious | Moderate | Low | Moderate |
| Gout attacks | Low | Low | Low | Serious | Moderate | Serious | Moderate |
| Perez-Ruiz, 2011 | | | | | | | |
| sUA and achieving sUA target | Serious | Low | Moderate | Serious | Low | Moderate | Low |
| Presence of tophi | Serious | Low | Moderate | Serious | Low | Low | Low |
| Body weight | Serious | Low | Moderate | Serious | Low | Low | Low |
| Gout attacks | Serious | Low | Moderate | Serious | Low | Serious | Low |
| Zhu, 2010* | | | | | | | |
| sUA and achieving sUA target | Serious | Moderate | Moderate | Serious | Moderate | Low | Moderate |
| Barskova, 2009 | | | | | | | |
| sUA and achieving sUA target | Critical | Low | Low | Serious | Moderate | Low | Moderate |
| Body weight (i.e. change in BMI) | Critical | Low | Low | Serious | Moderate | Low | Serious |
| Gout attacks | Critical | Low | Low | Serious | Moderate | Serious | Moderate |
| WDdtAEs | Critical | Low | Low | Serious | Moderate | Serious | Moderate |
| Friedman, 2008 | | | | | | | |
| Gout attacks | Critical | Low | Low | Serious | Low | Serious | Moderate |
| Dessein, 2000* | | | | | | | |
| sUA and achieving sUA target | Critical | Low | Low | Serious | Low | Low | Moderate |
| Body weight | Critical | Low | Low | Serious | Low | Serious | Moderate |
| Gout attacks | Critical | Low | Low | Serious | Low | Serious | Moderate |
| Brandstetter, 1986 | | | | | | | |
| sUA | Serious | Low | Low | Serious | Low | Low | Moderate |
| Body weight | Serious | Low | Low | Serious | Low | Low | Moderate |

| | | | | | | | | | |
|-----------------|-----------------------------------|----------------|----------------------------------|-----------------|-----------------------------------|------------|------------------------------|-----------|---------------------------|
| Critical | Critical risk of bias is present. | Serious | Serious risk of bias is present. | Moderate | Moderate risk of bias is present. | Low | Low risk of bias is present. | NI | No information available. |
|-----------------|-----------------------------------|----------------|----------------------------------|-----------------|-----------------------------------|------------|------------------------------|-----------|---------------------------|

Figure 3 Risk of bias summary figure. Similar outcomes has been put together in the figure but has been assessed separately. *Multiple publications existed. A primary publication was chosen. †Potentially serious risk of bias, since physical function was not reported in the article, but assessed low since data were provided from the author through email contact. BMI, body mass index; sUA, serum uric acid.

and they report one case of postoperative gout attack together with severe hyperuricaemia. Other factors increasing sUA levels are fasting,^{62–64} dehydration⁶⁵ and tissue hypoxia.⁶⁶ Fasting-associated increase in sUA is likely due to tissue breakdown.^{67,68} In line with this, daytime fasting during Ramadan, without weight

loss, compared with non-fasting did not increase sUA or gout attacks in gout patients.⁶⁹

Increased sUA seems to be related to decreased estimated glomerular filtration rate (eGFR).^{70,71} This is probably related to sUA affecting blood pressure,⁷² which may be caused by

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increased vascular stiffness.^{73 74} Reducing sUA may therefore have beneficial effect on susceptibility towards cardiovascular disease and diminished renal function.

In our study, we lacked evidence for many prespecified outcomes important to patients. Serum uric acid was among the most frequently reported outcomes and is recommended as a treatment target,^{15–19 21–23} since elevated sUA is considered to cause the disease. Gout attacks in this study is not well defined and was reported in various ways and over various follow-up times. Therefore, stating fewer gout attacks following weight loss is not very specific and not necessarily assessable in smaller study sizes, or when attacks were not systematically assessed. At least three studies^{27 43 45} did not point at reduced frequency of attacks, of which Friedman *et al*⁴³ did not report any baseline and Perez-Ruiz *et al*⁴⁵ did show less increase compared with control. Other studies can mask increasing number of attacks by reporting number of patients experiencing ≥ 1 attack over various follow-ups. Therefore, one could consider rating the evidence for gout attacks further down for indirectness.

Limitations of our methods include no independent double study selection, data extraction or risk of bias assessment. A limitation of investigating weight loss per se is that weight loss can be a consequence of many different interventions, that is, cointerventions, or conditions. Hence, it was impossible to ensure the weight reduction to be the only difference in terms of intervention from the comparison group, resulting in the inclusion of a wide variety of study settings. This is also observed as for which variables have been measured longitudinally. The included cohort studies stratifying according to weight loss may include unintentional weight loss for example, from illness, which is not relevant as intervention. Adding this to the fact that the majority of our included studies did not have a comparison group introducing non-controllable confounding, we cannot be sure that weight loss is accountable for all the effects observed. As a result, the implementation of weight loss intervention in clinical practice cannot be specified from the included studies. Taking the limitations of the available evidence into account, one may suggest, in order to address the effect of weight loss on sUA, that there currently is a need to perform a systematic review and meta-analysis of data not only for gout patients.

In conclusion, the available evidence is in favour of weight loss for overweight gout patients at medium-term/long-term follow-up on sUA, achieving sUA target and gout attacks. However, the evidence is of low, moderate and low quality, respectively. Harms were poorly reported. However, gout attacks might occur at short term when initiating treatment. We believe that there is an urgent need to initiate rigorous prospective studies (preferably RCTs) to provide more trustworthy estimates of gout-related benefits and harms including the effect on joint pain, tophi, physical function, HRQoL, adverse events and patient global assessment. Future research should aim at identifying the optimal magnitude and intensity of weight loss, the preferred method of weight loss, including prevention of flare, which cointerventions result in a better effect, and which gout patients will benefit the most, for example, grouped according to type (and possibly severity) of overweight and comorbidities.

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